PATENT SPECIFICATION

1,085,406

NO DRAWINGS **1,085,406**

Date of Application and filing Complete Specification: Sept. 29, 1964.
No. 39687/64.
Application made in United States of America (No. 316,141) on Oct. 14, 1963.
Application made in United States of America (No. 356,033) on March 31, 1964.
Complete Specification Published: Oct. 4, 1967.

Index at acceptance:—C2 C(1D, 1E3K4, 1E3K6, 1E4K4, 1E4K6, 1E5K4, 1E5K6, 1E6K4, 1E6K6, 1E7D1, 1E7D2, 1E7E1, 1E7E2, 1E7H2, 1E7L, 1E7N5, 1E7P3, 1F1A2, 1F1B, 1F1D3, 1G5A, 1G5B, 1G6B6, 1H1A1, 1H1A2, 1H1A3, 1H1B, 1H1C3, 1Q1A, 1Q2, 1Q4, 1Q5, 1Q6C, 1Q7A, 1Q7B, 1Q8A, 1Q8C, 1Q9A, 1Q9D1, 1Q9F1, 1Q9F2, 1Q9H, 1Q9L, 1Q11D, 1Q11G, 1Q11J, 2A1, 2A2, 2A3, 2A5, 2A7, 2B43A4, 2B43B4, 2B43D1, 2B43G1, 2D43A, 2D43B, 2D43C, 2D43D, 2D43E, 2D43F, 2D43J, 2D43S4, 2R15, 2R16, 2R17, 3A8A4, 3A8B2, 3A8C3, 3A8D2, 3A8K, 3A10E3A4, 3A10E3C4, 3A10E3D1, 3A10E5A, 3A10E5E, 3A13A1A4, 3A13A1C, 3A13A1L, 3A13A3A4, 3A13A3B1, 3A13A3B2, 3A13A3C, 3A13A3L, 3A13B3, 3A13C1C, 3A13C2C, 3A13C3C, 3A13C4C, 3A13C9, 3A13C10F,

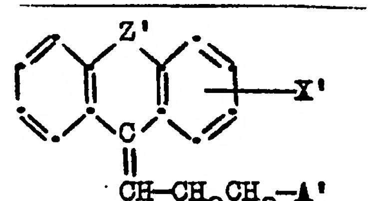
PATENTS ACT, 1949

SPECIFICATION NO. 1,085,406

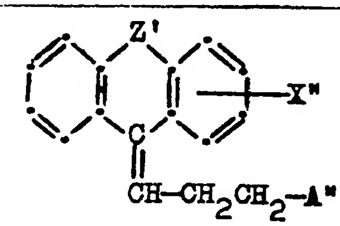
In accordance with the Decision of the Principal Examiner, acting for the Comptroller-General, dated 6 August 1969 this Specification has been amended under Section 33 in the following manner:-

Page 17, *before* "WHAT WE CLAIM IS:-"

insert "Reference is directed herein to Patent No. 858,187 which claims, *inter alia*, compounds having the formula



, wherein Z' is $-CH_2CH_2-$ or $-CH=CH-$, A' is a dialkylamino group and X' is a hydrogen or halogen atom or an alkyl or alkoxy group, acid addition salts thereof and a process for the manufacture of same, and to Patent No. 938,201 which claims, *inter alia*, compounds of the formula



, wherein Z' is $-CH_2CH_2-$ or $-CH=CH-$, A" is a (C_{1-4}-alkyl) amino group and X" is a hydrogen or halogen atom, acid addition salts thereof and a process for the manufacture of same."

THE PATENT OFFICE,
1st October 1969

D 119036/12

A19

1,085,406

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Int. Cl.:—C 07 f 9/54

COMPLETE SPECIFICATION

Aminoalkylphosphorus Compounds, preparation thereof and Reaction Products with Ketones

We, CHAS PFIZER & CO., INC., a Corporation organized under the laws of the State of Delaware, United States of America, of 235 East 42nd Street, New York 17, New York, United States of America, do hereby declare the invention, for which we pray that a Patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

This invention relates to organic compounds and to their use in the synthesis of valuable chemicals. More particularly, it is concerned with aminoalkyl tri-substituted-phosphonium compounds, with aminopropylidene tri-substituted-phosphoranes and with processes for their use in the preparation of aminopropylidene-substituted compounds. Such processes comprise the reaction of the compounds of this invention with ketones.

The aminoalkyl tri-substituted-phosphonium compounds contemplated by the present invention are those of the formula:

$$(R)_3P^{\oplus}—CH_2—CH(R_1)—CH_2—A.Hal^{\ominus}$$

wherein R is an alkyl group of from 1 to 6 carbon atoms, or a phenyl, aminophenyl or benzyl group,

R_1 is a hydrogen atom or an alkyl group of 1 to 6 carbon atoms, and

A is an amino, monoalkylamino, dialkylamino, piperidino, morpholino, piperazinyl, 4-alkylpiperazinyl, 4-hydroxyalkylpiperazinyl, 4-alkoxyalkylpiperazinyl, 4-aryloxyalkylpiperazinyl, 4-hydroxyalkyloxyalkylpiperazinyl, 4-alkylsulphonylpiperazinyl, 4-dialkylsulphamylpiperazinyl, mono-lower alkenylamino or mono-cycloalkylamino group, said alkyl, said lower alkenyl and said cycloalkyl groups containing up to 4 carbon atoms, said aryl groups containing 6, 7 or 8 carbon atoms, and acid addition salts of the said compounds and Hal is a halogen atom.

Particular mention is made of aminoalkyl triphenylphosphonium compounds of the formula:

$$(C_6H_5)_3P^{\oplus}—CH_2—CH_2—CH_2A'Hal^{\ominus}$$

[P

wherein A′ is an amino, monoalkylamino, dialkylamino, piperidino, morpholino, piperazinyl or 4-alkylpiperazinyl group, said alkyl groups containing 1 to 4 carbon atoms, and acid addition salts of said compounds with hydrohalic acids.

Special mention is made of two particularly valuable compounds in this series: 3-dimethylaminopropyl triphenylphosphonium bromide hydrobromide and 3 - (1 - piperazinopropyl)triphenylphosphonium bromide hydrobromide.

In addition, the present invention contemplates tri-substituted phosphine aminopropylidene phosphorane compounds of the formula:

$$(R)_3P=CH—CH(R_1)CH_2A$$

wherein R, R_1 and A have the meanings designated hereinbefore.

An especially valuable series of compounds is designated by the formula:

$$(C_6H_5)_3P=CH—CH_2—CH_2A'$$

wherein A′ has the meaning designated hereinbefore.

Particular mention is made of two compounds of the series which are particularly valuable for the purposes of preparing psychotherapeutic agents: (3-dimethylaminopropylidene-1)triphenylphosphorane and [3-(1-piperazino)propylidene-1] triphenylphosphorane.

The present invention, in addition, contemplates a process for the preparation of aminoalkylphosphorus compounds and their reaction products with ketones, in which a 3-halopropylphosphonium halide of the formula:

$$(R)_3P^{\oplus}—CH_2CH(R_1)CH_2Hal.Hal^{\ominus}$$

in which R is an alkyl group of 1 to 6 carbon atoms, or a phenyl, aminophenyl or benzyl group, and

R_1 is a hydrogen atom or an alkyl group of 1 to 6 carbon atoms, is reacted in an inert solvent with ammonia or an amine of the formula:

$$AH$$

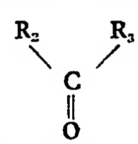
in which A is a monoalkylamino, dialkylamino, piperidino, morpholino, piperazinyl, 4-alkylpiperazinyl, 4-hydroxyalkylpiperazinyl, 4-alkoxyalkylpiperazinyl, 4-aryloxyalkylpiperazinyl, 4-hydroxyalkyloxyalkylpiperazinyl, 4-alkylsulphonylpiperazinyl, 4-dialkylsulphamylpiperazinyl, mono-lower alkenylamino, or mono-cycloalkylamino group, said alkyl, said lower alkenyl and said cycloalkyl groups containing up to 4 carbon atoms and said aryl groups containing 6, 7 or 8 carbon atoms, to form an aminoalkylphosphonium compound of the formula:

$$(R)_3P^{\oplus}—CH_2CH(R_1)CH_2A.Hal^{\ominus}$$

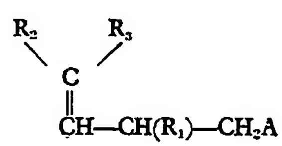
which, if desired, may be reacted with a strong base to form a phosphorane of the formula:

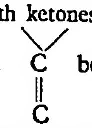
$$(R)_3P=CH—CH(R_1)CH_2A$$

which in turn, if desired, may be reacted with a ketone of the formula



in which R_2 and R_3 are each an alkyl group of 1 to 4 carbon atoms or, when taken together, form part of a ring system of from 3 to 7 members, to form an aminopropylidene of the formula:



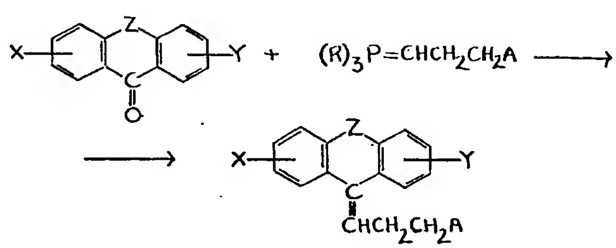
The phosphorus containing compounds of the present invention are valuable as plasticisers and fuel additives. The phosphoranes also particularly but not exclusively because of the —P=P— bond have value as monomers. The compounds produced by the reaction of phosphoranes with ketones are also of value as monomers, particularly but not exclusively because of the  bonding.

Moreover certain of the ketone reaction products have uses as therapeutic agents.

As is well known, many aminopropylidene-substituted compounds are valuable as psychotherapeutic agents. The said psychotherapeutic agents are used in the chemotherapy of mental diseases and especially for the treatment of depressed or excited states. Some of them are valuable in that they have potent antiemetic properties. Certain of the agents which can be prepared employing the valuable processes of the present invention are also of use as regulators of the autonomic nervous system and they may exhibit antiserotonin, antihistaminic and anticholinergic activity; they may also be appetite stimulants. The said psychotherapeutic agents are well known to those skilled in the art to which this invention pertains. For example, aminopropylidene dibenzoxepins are disclosed in Belgian Patent No. 641498 and aminopropylidene thioxanthenesulphonamides are disclosed in Belgian Patent No. 647066. The processes of the present invention are particularly useful in the preparation of the compounds disclosed in the said Belgian Patents.

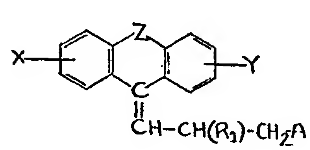
The aminopropylidene compounds have especially wide utility in that they can be converted to many useful derivatives by, for example, subsequent treatment of an unsubstituted nitrogen atom in the piperazine ring. By these subsequent reactions can be obtained aminopropylidene-substituted compounds of the above formula wherein the amino group is additionally a 4-acyloxyalkylpiperazinyl, 4-monoalkylcarbamylpiperazinyl, 4-dialkylcarbamylpiperazinyl, 4-acylalkylpiperazinyl, 4-aroylalkylpiperazinyl, 4-carboalkoxypiperazinyl, 4-carbamylpiperazinyl, 4-dialkylpiperazinyl, 4-acylpiperazinyl or 4-aroylpiperazinyl group. Some of the reaction products are therapeutically useful while others can be employed for other purposes, e.g. as monomers.

A particular embodiment of the process of the present invention is represented in the following sequence:



wherein Z is, for example, —O—, —S—, —CH_2CH_2—, —CH=CH—, —CH_2O—, —CH_2—S—, —NH— or —N(CH_3)—CH_2—, R and A are as hereinbefore defined and X and Y are, for example, hydrogen, alkyl, aryl, acyl, halogen, hydroxyl, sulphonamido, alkylthiosulphonamide, alkoxyl, trihalomethyl or aryloxyl. If the ring substituent is an acyl group, which shows some tendency to react with the organophosphorus reagent, it is preferred first to "protect" the said group by forming, for example, a ketal; then to carry out the process of the invention; then to regenerate the acyl group by removal of the "protecting" reagent, in accordance with standard procedures.

Thus the phosphoranes can be employed to prepare a dibenzoxepine or dibenzthiepine of the formula:



wherein R_1 is a hydrogen atom or an alkyl group of 1 to 4 carbon atoms; X and Y are each a hydrogen atom, an alkyl group of 1 to 4 carbon atoms, a chlorine, bromine,

iodine or fluorine atom, a trifluoromethyl group, an alkylthio group of 1 to 4 carbon atoms, an alkoxyl group of 1 to 4 carbon atoms, an acyl group of 1 to 4 carbon atoms or a hydroxyl group; Z is —CH_2O— or —CH_2S—; and A is a 4-alkylpiperazinyl, 4-hydroxyalkylpiperazinyl, 4-alkoxyalkylpiperazinyl, 4-arylpiperazinyl, 4-aryloxyalkylpiperazinyl, 4-hydroxyalkyloxyalkylpiperazinyl, 4-alkylsulphonylpiperazinyl, 4-dialkylsulphamylpiperazinyl, 4-dihydroxyalkylpiperazinyl, 4-halohydroxyalkylpiperazinyl, 4-acyloxyalkylpiperazinyl, 4-monoalkylcarbamylpiperazinyl, 4-dialkylcarbamylpiperazinyl, 4-acylalkylpiperazinyl, 4-aroylalkylpiperazinyl, 4-carboalkoxypiperazinyl, 4-carbamylalkylpiperazinyl, 4-monoalkylcarbamylalkylpiperazinyl, 4-dialkylcarbamylalkylpiperazinyl, 4-acylpiperazinyl or 4-aroylpiperazinyl group; the said alkyl, alkoxy and acyl groups containing from 1 to 4 carbon atoms and the said aryl, aryloxy and aroyl groups containing from 6 to 8 carbon atoms; *cis* and *trans* isomers thereof; and the acid-addition salts thereof.

Two specifically valuable compounds of the above formula are 11 - [3 - (4 - β - hydroxyethyl - 1 - piperazinyl) - propylidene] - 2 - chloro - 6,11 - dihydrodibenz (b,e)-oxepine, 11-[3-(4-monomethylcarbamylethyl-1-piperazinyl)-propylidene] - 2 - chloro-6,11-dihydrodibenz (b,e)-oxepine. The *cis* isomers of these compounds are particularly valuable.

As will be exemplified in detail hereinafter, the process is carried out by causing the alkylaminopropylidene tri-substituted-phosphorane contemplated by the present invention to be reacted with the appropriate ketone and, after allowing the reaction to continue for a period of time at an appropriate temperature, for example, from −10°C to 100°C depending on the reactivity of the ketone, the product can be isolated by removing the solvent such as, for example, by distillation in a vacuum. The product can be purified by recrystallisation and may be converted, if desired, to pharmaceutical dosage forms.

Also contemplated by the present invention is a process for the preparation of the aminopropylidene trisubstituted-phosphoranes from novel starting materials, tri-substituted aminoalkylphosphonium salts.

As will be exemplified, the reaction can be carried out in a medium such as dry tetrahydrofuran, which does not react with the reagents or the product. Appropriate strong bases comprise, for example, alkoxides or sodium hydride or organometallic reagents such as butyl lithium.

Heretofore, it has been proposed to prepare aminopropylidene compounds with psychotherapeutic properties by treatment of a ketone with an aminoalkylmagnesium halide Grignard reagent followed by hydrolysis and dehydration of the carbinol formed thereby. The Grignard technique is disclosed as a method for preparing the propylidene compounds of the two aforesaid Belgian patents and is well known in the art as a method for preparing other aminopropylidene compounds. In this connection, United States Patents Nos. 2,951,082, 2,996,503, 3,046,283, 3,047,580 and 3,055,888 show the use of the Grignard reagent. Among the advantages obtained in the process of the present invention is the preparation of certain aminopropylidene compounds more economically than can be done with the Grignard reagent or where it is not feasible to use the Grignard reagent. For example as is well known, Grignard reagents are often consumed in side reactions; these side reactions are avoided with the reagents of the invention. There is observed a selectivity of this reagent for ketone functions over ester and amide functions; this is greater than that of the Grignard reagent. Furthermore, this reagent allows direct introduction of the group:

$$=CH—CH_2—CH_2—R$$

wherein R is, for example, monomethylamino, amino or piperazinyl which is not possible with the Grignard reagent. A further and most important and unexpected advantage in using the compounds of the present invention has been to prepare therapeutically-active aminopropylidene compounds and to achieve a substantial degree of stereochemical control of the product. As is disclosed in Belgian Patent No. 641498, aminopropylidene-dibenzoxepines exist in two geometrical isomeric forms and one of the two aminopropylidene side chain configurations, *cis* and *trans*, is much more active pharmacologically. While the reason for this not clearly understood at this time, it appears that the compounds of the present invention generate the more active species. On the other hand, the Grignard reaction with the same ketone generates a mixture in which the isomer of lesser activity predominates. Thus, the reaction mixture from the use of the present process contains significantly greater activity than the reaction

mixture prepared from the Grignard process. Of course, where the ketone used is symmetrical, the products do not exhibit *cis/trans* configurations when prepared with either reagent. With respect to this effect, particular mention is made of the preparation, by this process, in high yield, of the more active isomer of 11 - (3 - dimethylamino - propylidene) - 6,11 - dihydrodibenz (b,e)oxepine, which active isomer is disclosed in Belgian Patent No. 641498. When the Grignard reagent is used, the isomer of lesser activity predominates; when the reagent of the present invention is used, the more active isomer predominates. In the said Belgian Patent the more active isomer is obtained by the classical and different fractional crystallisation technique from the Grignard mixture; the present process largely obviates fractional crystallisation.

The preparation of the compounds contemplated by the present invention is exemplified in detail hereinafter. The process involves the technique representable by the following three-step reaction sequence:

$$R_3P + Hal\text{—}CH_2CH(R_1)CH_2\text{—}Hal \xrightarrow[\text{100—160°C.}]{\text{Hydrocarbon solvent}} R_3P\oplus\text{—}CH_2CH(R_1)CH_2Hal.Hal^-$$

$$R_3P\oplus\text{—}CH_2CH(R_1)CH_2Hal\ .\ Hal^- \xrightarrow[\text{Ethanol, 20—30°C.}]{\text{AH}} R_3P\oplus\text{—}CH_2CH(R_1)CH_2A.H(Hal)_2^-$$

$$R_3P\oplus\text{—}CH_2CH(R_1)CH_2A.H(Hal)_2^- \xrightarrow{\text{Strong Base}} R_3P\oplus{=}CH\text{—}CH(R_1)CH_2\text{—}A$$

wherein R, R_1 and A have the meanings hereinbefore described and Hal represents a halogen atom. The starting materials for this sequence are readily available.

One method for preparing the compounds of the present invention is as follows: In the first step the appropriate substituted phosphine is treated with a stoichiometrically-equivalent amount of a 1,3-dihalopropane of the formula:

$$Hal\text{—}CH_2CH(R_1)CH_2Hal,$$

conveniently, dibromopropane, in the presence of a non-reactive organic solvent such as, for example, toluene or xylene. It is especially convenient to use about two volumes of xylene for each volume of the mixed phosphine and dihalopropane. The reaction mixture can be stirred in a nitrogen atmosphere at a reaction temperature above 100°C., preferably at 230°C, for a period of 20 hours. The product may be isolated by cooling the reaction mixture and collecting the 3-bromopropyltriphenylphosphonium bromide as a crystalline product. Alternatively, the reaction mixture may be subjected to a vacuum distillation to remove the solvent and the product remains as a residue.

For the second step in the sequence, the 3-halopropyltriphenylphosphonium halide may be dissolved in 4 volumes of a polar solvent, for example, methanol or ethanol, and treated with 2 equivalents or a slight excess of the appropriate amine. The reaction is completed by warming the mixture to 70°C, then allowing it to cool to room temperature. After 20 hours, the volatile components can be removed by distillation in a vacuum, then the residue may be dissolved in 3 volumes of hot ethanol and treated with gaseous hydrogen halide until the mixture becomes acidic. The product, a 3-aminopropyltri-substituted phosphonium halide hydrohalide, is isolated by filtration after concentration of the filtered reaction mixture to about one half of its original volume.

One method of carrying out the process of the present invention is as follows: An aminopropylidene trisubstituted-phosphorane compound is generated in solution by suspending the corresponding trisubstituted 3-aminopropyl phosphonium halide hydrohalide in an anhydrous open chain or cyclic ether, for example, diethyl ether or tetrahydrofuran. Alternatively, a solvent such as dimethylsulphoxide may be used. The solution is then treated with a strongly basic reagent at a ratio of 2 moles of said reagent per mole of said phosphonium halide hydrohalide. Among the reagents which may be employed are sodium methoxide, potassium *t*-butoxide, sodium hydride and butyl lithium. A particularly useful organometallic reagent is butyl lithium and it is convenient to add this as a heptane solution to the phosphonium halide hydrohalide

suspension during about one hour at room temperature. Rather than to isolate the product, which tends to be unstable, it is preferred to use it in the next step in solution by treating said solution with the appropriate ketone; those skilled in the art will recognise that this ordinarily is also done when the Grignard reagent is used.

The next step is carried out by adding 80% of one stoichiometric equivalent amount of the ketone and allowing the mixture to react for several hours. Depending on the reactivity of the ketone, the reaction rate is controlled by maintaining the mixture at any desired temperature within the range of from −10°C to 100°C. Water, 10% by volume, is then added and the organic solvent is removed under vacuum. The residue is treated with a mineral acid until strongly acidic (about pH 2) and there is added an organic solvent which is immiscible with water, preferably benzene. The suspension is stirred, the benzene is separated and the remaining mixture, comprising the product as its soluble or insoluble, depending on the ketone selected, hydrochloride salt and water, is made alkaline with sodium hydroxide solution and the liberated free base is extracted with benzene. The benzene extract is dried and the alkylaminopropylidene product is obtained by evaporation of the benzene. If desired, conversion of the free base into the acid addition salt may be effected.

When appropriate ketones are employed as hereinafter exemplified, compounds prepared by this process and their addition salts with pharmacologically acceptable acids may have interesting pharmacodynamic properties, which properties are useful in pharmaceutical compositions.

The salts contemplated by the present invention comprise generally acid addition salts. For example, the compounds form salts with hydrogen halides such as the hydrobromides and hydrochlorides and with sulphuric acid or phosphoric acid. In addition, valuable salts are formed with organic acids such as citric, acetic, lactic, maleic or formic.

The oxepins and thiepins in addition to being prepared by the organophosphorus process of this invention may also be prepared by the following techniques:

(a) Reaction of the appropriate oxepin-11-one or thiepin-11-one with an allyl magnesium halide Grignard reagent, followed by dehydration of the 11-hydroxy compound formed thereby and amination, with an appropriately-substituted piperazine, of the β-olefinic linkage of the compound; or

(b) Treatment of an oxepin-11-one or thiepin-11-one with an appropriate 3-piperazinylpropyne-1 in the presence of a condensing agent such as lithium amide followed by hydrogenation and dehydration of the subsequent intermediates.

However, such techniques do not give the predominantly *cis* isomer secured by the method employing the phosphorus compounds. Though the *cis* isomers predominate in the mixture prepared by the organophosphorus reaction, the pure *cis* isomers of the new compounds, can be obtained substantially free of the *trans* isomers by techniques, such as fractional crystallisation, which are well known to those skilled in the art.

The following detailed procedure illustrates the preparation of reagents employed in preparing the compounds of this invention.

Preparation

3-Bromopropyltriphenylphosphonium Bromide

Triphenylphosphine, 1.0 kg., and 770 g. of 1,3-dibromopropane are dissolved in 2.0 l of xylene and the solution is stirred under a nitrogen atmosphere at 130°C. After 20 hours the mixture is cooled, and the crystalline product, which precipitates, is collected and washed with 20 l of benzene. After drying *in vacuo* the product weighs 1578 g, m.p. 229—230°C; titration for bromide ion: Found, 17.1%; calcd., 17.2%.

The procedure is repeated substituting for 1,3-dibromopropane, a stoichiometrically-equivalent amount of 1,3-dibromo-2-methylpropane. There is obtained 3-bromo-2-methylpropyltriphenylphosphonium bromide. The 2-ethyl, 2-propyl and 2-butyl analogues are obtained in the same manner.

The procedure is repeated, substituting for the triphenylphosphine stoichiometrically-equivalent amounts of tributylphosphine, tri-*n*-hexylphosphine, tri-aminophenylphosphine and tribenzylphosphine; there are obtained, respectively, 3-bromopropyltributylphosphonium bromide, 3-bromopropyl-tri-*n*-hexylphosphonium bromide, 3-bromopropyl triaminophenylphosphonium bromide and 3-bromopropyltribenzylphosphonium bromide.

The procedure is repeated substituting for 1,3-dibromopropane, a stoichiometrically-equivalent amount of 1,3-dichloropropane; there is obtained 3-chloropropyltri-

phenylphosphonium chloride. In a similar manner, substituting 1,3-diiodopropane, there is obtained 3-iodopropyltriphenylphosphonium iodide.

The following Examples illustrate the process of this invention and the compounds advantageously prepared thereby.

EXAMPLE I

3-Dimethylaminopropyltriphenylphosphonium bromide hydrobromide

A solution of 595 g of anhydrous dimethylamine and 1358 g of 3-bromopropyltriphenylphosphonium bromide in 4 litres of ethanol is warmed to 70°C until solution is complete and the solution then is allowed to stand at room temperature for 20 hours. Volatile components are removed by distillation in a vacuum and the residue is suspended in 2.0 l of ethanol and is redistilled to remove excess amine. The residue is dissolved in 3.0 l of warm ethanol and gaseous hydrogen bromide is passed into the solution until the mixture is acidic. After filtration the solution is concentrated to a volume of 3.0 l, is cooled, whereupon the product precipitates, and the precipitate is collected; it weighs 1265 g, m.p. 274—281°C. Recrystallisation from ethanol raises the melting point to 280.5°—282.5°C. Bromide ion titration: Found, 31.2%; calcd. 31.3%.

EXAMPLE II

3-Methylaminopropyltriphenylphosphonium bromide hydrobromide

3-Bromopropyltriphenylphosphonium bromide (25.0 g), 13.2 g methylamine and 120 ml methanol are mixed and reacted by the procedure of Example I. There is obtained 19.0 g of product, m.p. 279°—281°C. Bromide ion titration: Found, 32.3%; calcd., 32.4%.

EXAMPLE III

3-Aminopropyltriphenylphosphonium bromide hydrobromide

3-Bromopropyltriphenylphosphonium bromide (100 g) and 21.9 g anhydrous ammonia are dissolved in 500 ml ethanol and the reaction is carried out according to the procedure of Example I. Recrystallisation from ethanol removes a small amount of *bis*-alkylation by-product from the crude reaction residue and the desired mono adduct is recovered from the crystallisation liquors, m.p. 260°—262.5°. Bromide ion titration: Found, 32.6%; calcd. 33.2%.

EXAMPLE IV

3-(1-Piperazinopropyl)-triphenylphosphonium bromide hydrobromide

To a solution of piperazine hydrobromide (from 172 g anhydrous piperazine, 2.5 l of 80% ethanol and 227 ml 48% hydrobromic acid) at 60° is added 464 g of 3-bromopropyltriphenylphosphonium bromide in a single portion and the resulting mixture is heated at reflux for 5.5 hours. After evaporation of the volatile components *in vacuo* the residue is digested with 5 litres of ethanol at reflux and the insoluble piperazine dihydrobromide is removed by filtration. The alcohol filtrate is concentrated to 2.5 l is cooled to 10°C and the product which separated is isolated by filtration: it weighs 363 g, m.p. 278—283°C. An additional 108 g is isolated by further concentration of the liquors.

EXAMPLE V

By the procedure of the designated Examples, substituting appropriately substituted phosphonium halides and amines, the following additionally substituted 3-aminopropyltriphenylphosphonium halide hydrohalides are prepared:

$$(R)_3P^{\oplus}\text{—}CH_2CH(R_1)CH_2AHal^{\ominus}.H.Hal$$

Procedure of Example	R	R_1	A
I	C_6H_5	H	$\text{—}N(H)CH_2CH_2CH_2CH_3$
I	C_6H_5	H	$\text{—}N(CH_2CH_2CH_2CH_3)_2$
I	C_6H_5	$CH_2CH_2CH_2CH_3$	$\text{—}N(CH_3)_2$
IV	C_6H_5	H	$\text{—}N\text{—}CH_2CH_2OCH_2CH_2$

Procedure of Example	R	R_1	A
IV	C_6H_5	H	$-N-CH_2CH_2CH_2CH_2CH_2$
I	$CH_3CH_2CH_2CH_2$	H	$-N(CH_3)_2$
I	$CH_3(CH_2)_5-$	H	$-N(CH_3)_2$
I	$C_6H_5CH_2$	H	$-N(CH_3)_2$
I	C_6H_5	H	$-N(CH_3)CH_2CH=CH_2$
I	C_6H_5	H	$-N(CH_3)CHCH_2CH_2$
III	C_6H_5	CH_3	$-NH_2$
IV	C_6H_5	H	$-NCH_2CH_2N(CH_3)CH_2CH_2$
IV	C_6H_5	H	$-NCH_2CH_2N(CH_2CH_2CH_3)CH_2CH_2$
IV	C_6H_5	H	$-NCH_2CH_2N(CH_2CH_2OCH_2CH_3)CH_2CH_2$
IV	C_6H_5	H	$-NCH_2CH_2N(CH_2CH_2OC_6H_5)CH_2CH_2$
IV	C_6H_5	H	$-NCH_2CH_2N(CH_2CH_2OCH_2CH_2OH)CH_2CH_2$
IV	C_6H_5	H	$-NCH_2CH_2N(SO_2CH_2CH_2CH_3)CH_2CH_2$
IV	C_6H_5	H	$-NCH_2CH_2N[SO_2N(CH_2CH_3)_2]CH_2CH_2$
IV	C_6H_5	H	$-NCH_2CH_2N(CH_2CH_2CH_2CH_3)CH_2CH_2$

When the bromo-tri-substituted phosphonium bromide starting material is used, the above compounds are obtained as bromide hydrobromides. Similarly, use of the chloro-tri-substituted phosphonium chloride and iodo-tri-substituted phosphonium iodide leads, respectively, to chloro hydrochlorides and iodo hydroiodides.

Example VI

The preparation of the aminopropylidene tri-substituted-phosphorane compounds of the present invention is carried out by the following procedure: Anhydrous 3-dimethylaminopropyltriphenylphosphonium bromide hydrobromide prepared as described in Example I, 1530 g, is suspended in 4.5 l of dry tetrahydrofuran and 6.0 moles of butyl lithium in heptane solution is added during one hour. There is generated, *in situ*, 3-dimethylaminopropylidene triphenylphosphorane, which is suitable for reaction with an appropriately-substituted ketone to prepare the aminopropylidene compounds with valuable psychotherapeutic properties as disclosed in the above-mentioned Belgian and United States patents. In a similar manner, there are prepared the following aminopropylidene tri-substituted phosphorane compounds:

$$(R)_3P=CHCH(R_1)CH_2A$$

$(R)_3P{=}CHCH(R_1)CH_2A$

R	R_1	A
C_6H_5	H	$-NH(CH_3)$
C_6H_5	H	$-NH_2$
C_6H_5	H	$-NCH_2CH_2NHCH_2CH_2$
C_6H_5	H	$-N(H)CH_2CH_2CH_2CH_3$
C_6H_5	H	$-N(CH_2CH_2CH_2CH_3)_2$
C_6H_5	$CH_2CH_2CH_2CH_3$	$-N(CH_3)_2$
C_6H_5	H	$-NCH_2CH_2OCH_2CH_2$
C_6H_5	H	$-NCH_2CH_2CH_2CH_2CH_2$
$CH_3CH_2CH_2CH_2$	H	$-N(CH_3)_2$
$CH_3(CH_2)_5$	H	$-N(CH_3)_2$
$C_6H_5CH_2$	H	$-(CH_3)_2$
C_6H_5	H	$-N(CH_3)CH_2CH{=}CH_2$
C_6H_5	H	$-N(CH_3)CHCH_2CH_2$
C_6H_5	CH_3	$-NH_2$
C_6H_5	H	$-NCH_2CH_2N(CH_3)CH_2CH_2$
C_6H_5	H	$-NCH_2CH_2N(CH_2CH_2CH_3)CH_2CH_2$
C_6H_5	H	$-NCH_2CH_2N(CH_2CH_2OCH_2CH_3)CH_2CH_2$
C_6H_5	H	$-NCH_2CH_2N(CH_2CH_2OC_6H_5)CH_2CH_2$
C_6H_5	H	$-NCH_2CH_2N(CH_2CH_2OCH_2CH_2OH)CH_2CH_2$
C_6H_5	H	$-NCH_2CH_2N(SO_2CH_2CH_2CH_3)CH_2CH_2$
C_6H_5	H	$-NCH_2CH_2N[SO_2N(CH_2CH_3)_2]CH_2CH_2$
C_6H_5	H	$-NCH_2CH_2N(CH_2CH_2CH_2CH_3)CH_2CH_2$

EXAMPLE VII

11-(3-Dimethylaminopropylidene)-6,11-dihydrodibenz-(b,e) oxepin

Anhydrous 3-dimethylaminopropyltriphenylphosphonium bromide hydrobromide

prepared as in Example I, 1530 g, is suspended in 4.5 1 dry tetrahydrofuran and 6.0 moles of butyl lithium in heptane is added during 1 hour. After an additional 30 minutes, 483 g of 6,11 - dihydrodibenz - (b,e) oxepin - 11 - one, prepared as described in Belgian Patent No. 641498, is added to the deep red solution and the reaction was maintained at reflux for 10 hours. Water, 500 ml, is added at room temperature and the solvent is removed *in vacuo*. The crude residue is treated with 10% hydrochloric acid until acidic (pH 2) and then 1.5 1 benzene is added. After stirring, the mixture separates into three phases (an insoluble hydrochloride salt product phase, an aqueous phase and an oragnic phase). The benzene layer is removed by decantation and the remaining mixture is rendered basic with 10% sodium hydroxide solution and is extracted with 3 1500 ml portions of benzene. The benzene extracts are washed, then dried with anhydrous sodium sulphate and concentrated in a vacuum leaving a residue of 1530 g, gas and thin-layer chromatography analysis show this to be a *cis/trans* mixture (approx. 4:1) of 11-dimethylaminopropylidene-6,11-dihydrodibenz (b,e)oxepin (90% yield). This mixture has substantially more activity pharmacologically than the *cis/trans* mixture obtained by the Grignard route disclosed in the Belgian Patent No. 641498.

Example VIII

11-(3-Dimethylaminopropylidene)-2-chloro-6,11-dihydrodibenz(b,e)-oxepin

By the procedure of Example VII, 43.6 g of dimethylaminopropyltriphenylphosphonium bromide hydrobromide, 176 ml of tetrahydrofuran, 0.172 mole of butyl lithium and 17.2 g of 2 - chloro - 6,11 - dihydrodibenz - (b,e) - oxepin - 11 - one leads to 22.0 g of product. One of the isomers is isolated by crystallisation of the hydrochloride salt from chloroform-carbon tetrachloride, m.p. 228°—230°C.

Anal. Calcd. for $C_{19}H_{21}ONCl_2$:	C, 65.14;	H, 6.04;	N, 4.00
Found:	C, 64.84;	H, 5.95;	N, 3.91.

Example IX

11-(3-Dimethylaminopropylidene)-9-chloro-6,11-dihydrodibenz(b,e)-oxepin

3-Dimethylaminopropyltriphenylphosphonium bromide hydrobromide, 2.60 g, 1.0 g of 9 - chloro - 6,11 - dihydrodibenz(b,e) - oxepin - 11 - one, 10 ml of dry tetrahydrofuran and 0.0102 mole of butyl lithium reacted by the procedure of Example VII leads to 1.28 g crude product as a mixture of geometric isomers. One of the pure isomers, 450 mg, m.p. 220°—222°C, is isolated by fractional crystallisation of the hydrochloride salt from ethanol-ether.

Example X

11-(3-Dimethylaminopropylidene)-2-dimethylsulphamyl-6,11-dihydrodibenz (b,e)-oxepin

3-Dimethylaminopropyltriphenylphosphonium bromide hydrobromide, 24.5 g, 100 ml of dry tetrahydrofuran, 0.096 mole butyl lithium and 12.0 g 2 - dimethylsulphamyl - 6,11 - dihydrodibenz - (b,e) oxepin - 11 - one reacted by the procedure of Example VII leads to 15.6 g product as a *cis/trans* mixture. Crystallisation of the hydrochloride salts from ethanol affords 6.8 g of one isomer, m.p. 225°—227°C and 1.0 g of the other isomer, m.p. 214—217°.

Anal. Calcd. for $C_{21}H_{27}O_3N_2SCl$:	C, 59.63;	H, 6.43.
Found: (first isomer) :	C, 59.54;	H, 6.44.
Found: (second isomer) :	C, 59.62;	H, 6.42.

Example XI

10-(3-Dimethylaminopropylidene)thioxanthene

3-Dimethylaminopropyltriphenylphosphonium bromide hydrobromide, 7.64 g, 50 ml of dry THF, 0.030 mole of butyl lithium and 2.12 g of thiaxanthenone by the procedure of Example VII and a reaction period of 1 hours leads to 1.6 g of product as the hydrochloride, m.p. 180°—183°. This material is physically identical with the same product prepared by the Grignard reaction.

Example XII

10-(3-Dimethylaminopropylidene)-2-chlorothioxanthene

The procedure of Example VII with 2.47 g of 2-chlorothiaxanthen-10-one leads to *cis/trans* mixture of product as the hydrochloride, m.p. 187—191°.

EXAMPLE XIII

Reaction of 3-Amino- and 3-methylaminopropyltriphenylphosphonium bromide hydrobromide with 6,11-dihydrodibenz-(b,e)-oxepin-11-one

3-Methylaminopropyltriphenylphosphonium bromide hydrobromide, 6.0 g, suspended in 50 ml of dry tetrahydrofuran is treated with 0.024 mole of butyl lithium and then 1.88 g ketone as in Example VII. The basic product, as a mixture of geometric isomers, weighs 2.1 g; from this mixture one pure isomer, 990 mg, m.p. 223°—225°, is isolated by recrystallisation with ethanol-ether. The procedure is repeated substituting a stoichiometrically-equivalent amount of 3-aminopropyltriphenylphosphonium bromide hydrobromide; there is obtained 11-(3-aminopropylidene)-6,11-dihydrodibenz-(b,e)oxepin.

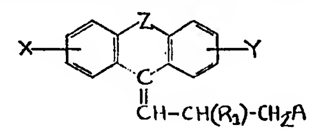
EXAMPLE XIV

11-(3-Piperazinopropylidene)-2-chloro-6,11-dihydrodibenz-(b,e)-oxepin

To a suspension of 71.5 g of the phosphonium salt of Example VII in 220 ml of dry tetrahydrofuran is added 120 ml of 2.62 *M* butyl lithium in heptane during one hour followed in 30 minutes by 25.0 g 2 - chloro - 6,11 - dihydrodibenz - (b,e) - oxepin - 11 - one. After 15.5 hours at reflux the basic reaction product is isolated in the manner described in Example VII; 33.8 g viscose oil. A crystalline dihydrochloride of this material, 2 - chloro - 11 - (3 - piperazino - propylidene) - 6H - dibenzo - (b,e)oxepin, prepared in methanol ether, melted at 189—193°C and was found to be a mixture of *cis/trans* isomers.

EXAMPLE XV

By the procedure of Example VIII, substituting for the 6H-dibenz-(b,e)oxepin, 11-one, stoichiometrically-equivalent amounts of other appropriately substituted ketones and using the appropriately substituted amino propylphosphonium halide salt there are obtained the following additional aminopropylidene compounds:



Z	X	Y	R_1	A
—O—	H	H	H	$—N(CH_3)_2$
—S—	H	H	H	$—NHCH_3$
$—CH_2CH_2—$	H	H	H	$—N(CH_3)_2$
—CH=CH—	H	H	H	$—N(CH_3)_2$

Z	X	Y	R_1	A
$—CH_2S—$	H	H	H	$—N(CH_3)_2$
—NH—	H	H	H	$—N(CH_3)_2$
$—N(CH_3)CH_2—$	H	H	H	$—N(CH_3)_2$
$—CH_2O—$	H	H	CH_3	$—N(CH_3)_2$
—S—	9—Cl	H	H	$—N(CH_3)_2$
—S—	H	2—Br	H	$—N(CH_3)_2$
$—CH_2O—$	H	H	H	$—NH(CH_3)$
$—CH_2O—$	H	H	H	$—NH_2$
$—CH_2O—$	H	H	H	$—N(H)CH_2CH_2CH_2CH_3$
$—CH_2O—$	H	H	H	$—N(CH_2CH_2CH_2CH_3)_2$
$—CH_2O—$	H	H	$CH_2CH_2CH_2CH_3$	$—N(CH_3)_2$
$—CH_2O—$	H	H	H	$—N(CH_3)CH_2CH{=}CH_2$
$—CH_2O—$	H	H	H	$—N(CH_3)CHCH_2CH_2$
$—CH_2O—$	H	H	CH_3	$—NHC_2$
$—CH_2O—$	H	H	H	$—NCH_2CH_2N(CH_2CH_2CH_3)CH_2CH_2$
$—CH_2O—$	9—OH	H	H	$—NCH_2CH_2OCH_2CH_2$
$—CH_2O—$	H	2—Br	H	$—NCH_2CH_2N(CH_3)CH_2CH_2$
$—CH_2O—$	9—Cl	H	H	$—NCH_2CH_2N(CH_3)CH_2CH_2$
$—CH_2O—$	H	2—Cl	CH_3	$—NCH_2CH_2N(CH_2CH_2OCH_2CH_3)CH_2CH_2$

Z	X	Y	R_1	A
$—CH_2O—$	$7—CH_2CH_2CH_2CH_2CH_3$	H	H	$—NCH_2CH_2N(CH_2CH_2OC_6H_5)CH_2CH_2$
$—CH_2O—$	$7—CH_3$	2—I	H	$—NCH_2CH_2N(CH_2CH_2OCH_2CH_2OH)CH_2CH_2$
$—CH_2CH_2$	$8—CH_3CH_2CH_2$	H	H	$—NCH_2CH_2NHCH_2CH_2$
$—CH{=}CH—$	H	$2—CF_3$	H	$—NCH_2CH_2N(CH_3(CH_2CH_2$
$—CH_2S—$	$8—CH_3CH_2CH_2S$	H	H	$—NCH_2CH_2N(CH_3)CH_2CH_2$
—NH—	H	$2—CH_3CH_2CH_2CH_2O—$	H	$—NCH_2CH_2CH_2CH_2CH_2$
$—CH_2O—$	H	2—Cl	H	$—NCH_2CH_2N(CH_3)CH_2CH_2$
$—CH_2O—$	H	H	H	$—NCH_2CH_2N(SO_2CH_2CH_2CH_3)CH_2CH_2$
$—CH_2O—$	H	H	H	$—NCH_2CH_2N[SO_2N(CH_2CH_3)_2]CH_2CH_2$
$—CH_2O—$	H	H	H	$—NCH_2CH_2N(CH_2CH_2OCH_2CH_2OH)CH_2CH_2$
$—CH_2O—$	H	H	H	$—NCH_2CH_2N(CH_2CH_2CH_2CH_3)CH_2CH_2$

EXAMPLE XVI

By the procedure of Example VIII substituting stoichiometrically-equivalent amounts of the appropriate ketones and using the appropriately substituted aminopropylphosphonium halide salt the following additional aminopropylidene compounds are prepared:

$$R_2R_3C{=}CH{-}CH(R_1)CH_2{-}A$$

R_2	R_3	R_1	A
CH_3	CH_3	H	$—NH_2$
CH_3	CH_3	H	$—N(H)CH_3$
CH_3	CH_3	H	$—N(CH_3)_2$
$—CH_2CH_2—$		H	$—N(CH_3)_2$
$—CH_2CH_2CH_2—$		H	$—N(CH_3)_2$
$—CH_2CH_2CH_2CH_2—$		H	$—N(CH_3)_2$
$—CH_2CH_2CH_2CH_2CH_2—$		H	$—N(CH_3)_2$
$—CH_2CH_2CH_2CH_2CH_2CH_2—$		H	$—N(CH_3)_2$
$—CH_2CH_2CH_2CH_3$	$—CH_2CH_2CH_2CH_3$	$—CH_2CH_2CH_2CH_3$	$—N(CH_3)_2$
CH_3	CH_3	H	$—NCH_2CH_2NHCH_2CH_2$
CH_3	CH_3	H	$—NCH_2CH_2N(CH_2CH_2CH_2CH_3)CH_2CH_2$

Example XVII

The procedure of Example VII is repeated substituting, respectively, for *n*-butyl lithium other strong bases: sodium hydride, sodium methoxide and potassium-*tert*-butoxide. The desired aminopropylidene dibenzoxepin is obtained.

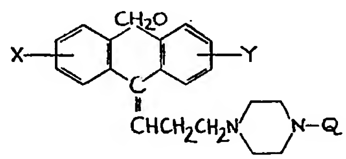
The procedure of Example VI is repeated substituting for the dry tetrahydrofuran, respectively, the same weight of dry diethyl ether, dry dimethoxy ethane and dry dimethylsulphoxide. There are obtained the desired aminopropylidene tri-substituted-phosphorane compounds.

Example XVIII

11-[3-(4-Monomethylcarbamylethyl-1-piperazinyl)-propylidene]-2-dimethylsulphonamido-6,11-dihydrodibenz (b,e)-oxepin

The appropriate piperazine of Example XV, 2.7 g, dimethylformamide, 16 ml, and N-methyl-β-chloropropionamide, 2.4 g, are mixed with 2.72 g of potassium carbonate and the mixture is heated at 75°C for 45 hours; there is added an additional 1.2 g of the chloroamide and heating is continued for a total of 69 hours. The reaction mixture is poured into water, is rendered basic, and the liberated base is extracted with benzene. The base is converted to a dihydrochloric acid addition salt with ethanol and hydrogen chloride. Recrystallisation from ethanol yields 2.5 g, m.p. 222°—224°C.

By the same procedure substituting appropriate piperazinyl propylidene compounds and haloalkylamides, there are obtained the following piperazinyl propylidene compounds:



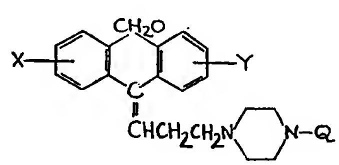
Y	X	Q
H	H	—$CH_2CH_2CH_2CONH_2$
H	H	—$CH_2CH_2CON(CH_3)_2$
H	2—Cl	—$CH_2CH_2CON(CH_3)_2$
H	2—Cl	—CH_2CONH_2

Example XIX

11-[3-(4-β-Hydroxyethyl-1-piperazinyl)-propylidene]-2-chloro-6,11-dihydrodibenz (b,e)-oxepin

5.1 g of the piperazine base of Example XIV is dissolved in 100 ml of methanol. One ml of ethylene oxide is added and the reaction mixture is refluxed for 2 hours. The solvent is evaporated and the residue is dissolved in ethanol. The solution is treated with an excess of hydrogen chloride in ethanol and the solvents are evaporated leaving the product in the form of its dihydrochloride salt. There is obtained 6 g of product, m.p. 253°—255°C; recrystallisation from ethanol-water increases the purity: m.p. 257°—259°C.

By the same procedure substituting appropriate piperazines and carrying out, as necessary, subsequent derivatisation reactions, such as reaction with acetic anhydride, or benzoylation, there are obtained the following compounds:



X	Y	Q
H	H	—$CH_2CH_2OCOCH_3$
H	H	—$CH_2CH_2OCOC_6H_5$
H	H	—$CH_2CH(OH)CH_3$
H	H	—$CH_2CH(OCOCH_3)CH_3$

Example XX

The piperazine of Example XIV, 1.85 g, 1.2 g of potassium iodide and 1.04 g of potassium carbonate is treated with 0.84 g of 3 - chloro - 1,2 - propanediol and there is added 25 ml of isoamylalcohol. The reaction mixture is heated to 100°C for 20 hours. There is added another 0.84 g of the propanediol and the reaction mixture is heated at 100°C for an additional 7 hours. The mixture is cooled, diluted with water and extracted with benzene. The benzene layer is washed, dried and evaporated to give an oil which is dissolved in ethanol, acidified with ethereal hydrogen chloride and the crystals are collected. Recrystallisation from water affords 1 g, m.p. 253°—255°C, of 11 - {3 - [4 - (2′,3′ - dihydroxy)propyl - 1 - piperazinyl] - propylidene} - 2 - chloro - 6,11 - dihydrodibenz (b,e) - oxepin.

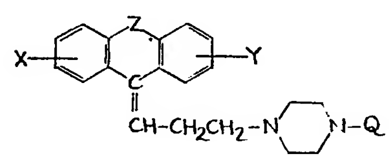
Example XXI

1.7 g of the piperazine of Example XIV, is mixed with 0.95 g of potassium carbonate, 0.95 g of epibromohydrin and 25 ml of ethanol. The mixture is stirred at room temperature for 20 hours, then the solvent is evaporated. The residue is partitioned between benzene and water, the benzene layer is separated, dried and evaporated. The residue, 1.92 g., is converted to the dihydrochloride with excess hydrogen chloride in ethanol, during which the oxirane ring opens. The solvents are evaporated and the residue is crystallized from ethanol-water, m.p., 256°—259°C. There is thus obtained 11 - {3 - [4 - (2′ - chloro - 3′ - hydroxy)propyl - 1 - piperazinyl] - propylidene} - 2 - chloro - 6,11 - dihydrodibenz (b,e)-oxepin.

Example XXII

The acyloxyalkylpiperazinyl compounds of this invention are prepared by treating the hydroxyalkyl compounds with an acetylating agent, e.g., acetic anhydride; the acylalkylpiperazinyl and aroylalkylpiperazinyl compounds are prepared by treating the unsubstituted piperazinyl compounds with an appropriate haloalkylamide in the presence of an acid acceptor; the carboalkoxypiperazinyl compounds are prepared by treating the unsubstituted piperazinyl compounds with an alkylchloroformate in the presence of a basic reagent; the acylpiperazinyl and aroylpiperazinyl compounds are obtained by treating the unsubstituted piperazinyl compounds with an acyl halide such as acetyl chloride or with an aroyl halide such as benzoyl chloride; the carbamylpiperazinyl (mono and dialkyl) compounds of this invention are prepared by treating the unsubstituted piperazinyl compounds with an excess of phosgene followed by the appropriate amine.

By these procedures there are prepared compounds of the following formula:



Z	X	Y	Q
$-CH_2O-$	H	$2-CH_3CO-$	$-CH_2CH_2OCO-CH_3$
$-CH_2O-$	H	H	$-CH_2CH_2CO-C_6H_4CH_3$
$-CH_2O-$	H	$2-CH_3CH_2CH_2CO-$	$-\overset{\overset{O}{\Vert}}{C}-OCH_2CH_3$
$-CH_2O-$	H	$2-Cl$	$-COCH_3$
$-CH_2O-$	H	$2-Cl$	$-COC_6H_5$
$-CH_2S-$	H	H	$-CH_2CH_2OH$
$-CH_2S-$	H	H	$-CH_2CH_2O-CH_2CH_3$
$-CH_2S-$	H	H	$-C_6H_5$
$-CH_2S-$	H	H	$-CH_2CH_2OC_6H_5$
$-CH_2S-$	H	H	$-CH_2CH_2OCH_2CH_2OH$
$-CH_2S-$	H	H	$-SO_2CH_3$
$-CH_2S-$	H	H	$-SO_2N(CH_3)_2$
$-CH_2S-$	H	H	$-CH_2CH(OH)CH_2OH$
$-CH_2S-$	H	H	$-CH_2CH(Cl)CH_2OH$
$-CH_2S-$	H	H	$-CH_2CH_2OCOCH_3$
$-CH_2S-$	H	H	$-\overset{\overset{O}{\Vert}}{C}-NHCH_3$
$-CH_2S-$	H	H	$-\overset{\overset{O}{\Vert}}{C}-N(CH_3)_2$
$-CH_2S-$	H	H	$-CH_2CH_2COCH_3$
$-CH_2S-$	H	H	$-CH_2CH_2COC_6H_5$
$-CH_2S-$	H	H	$-COOC_2H_5$
$-CH_2S-$	H	H	$-CH_2CH_2CONH_2$
$-CH_2S-$	H	H	$-CH_2CH_2CONHCH_3$
$-CH_2S-$	H	H	$-CH_2CH_2CON(CH_3)_2$
$-CH_2S-$	H	H	$-COCH_3-$
$-CH_2S-$	H	H	$-COC_6H_5$

WHAT WE CLAIM IS:—

1. A process for the preparation of aminoalkylphosphorus compounds and their reaction products with ketones, in which a 3-halopropylphosphonium halide of the formula:

$$(R)_3P^{\oplus}—CH_2CH(R_1)CH_2Hal.Hal^{\ominus}$$

in which Hal is a halogen atom, R is an alkyl group of 1 to 6 carbon atoms, or a phenyl, aminophenyl or benzyl group, and R_1 is a hydrogen atom or an alkyl group of 1 to 6 carbon atoms, is reacted in an inert solvent with ammonia or an amine of the formula:

$$AH$$

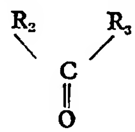
in which A is a monoalkylamino, dialkylamino, piperidino, morpholino, piperazinyl, 4-alkylpiperazinyl, 4-hydroxyalkylpiperazinyl, 4-alkoxyalkylpiperazinyl, 4-aryloxy-alkylpiperazinyl, 4-hydroxyalkyloxyalkylpiperazinyl, 4-alkylsulphonylpiperazinyl, 4-dialkylsulphamylpiperazinyl, mono-lower alkenylamino, or mono cycloalkylamino group, said alkyl, said lower alkenyl and said cycloalkyl groups containing up to 4 carbon atoms and said aryl groups containing 6, 7 or 8 carbon atoms, to form an aminoalkylphosphonium compound of the formula:

$$(R)_3P^{\oplus}—CH_2CH(R_1)CH_2A.Hal^{\ominus}$$

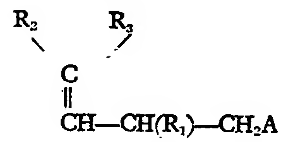
which, if desired, may be reacted with a strong base to form a phosphorane of the formula:

$$(R)_3P=CH—CH(R_1)CH_2A$$

which in turn, if desired, may be reacted with a ketone of the formula:

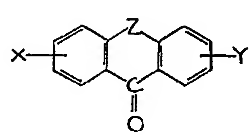


in which R_2 and R_3 are each an alkyl group of 1 to 4 carbon atoms or, when taken together, form part of a ring system of from 3 to 7 members, to form an amino-propylidene of the formula:



2. A process according to claim 1, in which R_1 is a hydrogen atom and R is a phenyl group.

3. A process according to either one of claims 1 and 2, in which the said ketone is a compound of the formula:



in which X and Y are each a hydrogen or halogen atom or an alkyl, aryl, hydroxyl, sulphonamide, alkoxy, trihalomethyl or aryloxy group, and Z is —O—, —S—, $—CH_2CH_2—$, —CH=CH—, $—CH_2O—$, $—CH_2S—$, —NH— or $—N(CH_3)—CH_2—$.

4. A process according to claim 1, in which the 3-halopropylphosphonium halide is prepared by reaction in an inert organic solvent of a phosphine of the formula:

$$(R)_3P$$

with a 1,3-dihalopropane of the formula:

$$Hal—CH_2CH(R_1)CH_2Hal$$

in which R and R_1 have the same meanings as set out in claim 1.

5. An aminoalkylphosphorus compound having the formula:

$$(R)_3P^{\oplus}—CH_2—CH(R_1)—CH_2—A.Hal^{\ominus}$$

wherein Hal is a halogen atom, R is an alkyl group of 1 to 6 carbon atoms, or a phenyl, aminophenyl or benzyl group, R_1 is a hydrogen atom or an alkyl group of 1 to 6 carbon atoms, and A is an amino monoalkylamino, dialkylamino, piperidino, morpholino, piperazinyl, 4-alkylpiperazinyl, 4-hydroxyalkylpiperazinyl, 4-alkoxyalkylpiperazinyl, 4-aryloxyalkylpiperazinyl, 4-hydroxyalkyloxyalkylpiperazinyl, 4-alkylsulphonylpiperazinyl, 4-dialkylsulphamylpiperazinyl, mono-lower alkenylamino or monocycloalkylamino group, said alkyl, said lower alkenyl and said cycloalkyl groups containing up to 4 carbon atoms, and said aryl groups containing 6, 7 or 8 carbon atoms, and acid addition salts of the said compounds.

6. An aminoalkylphosphorus compound according to claim 5, wherein R is a phenyl group, R_1 is a hydrogen atom and A is an amino monoalkylamino, dialkylamino, piperidino, morpholino, piperazinyl, or 4-alkylpiperazinyl group, said alkyl groups containing 1 to 4 carbon atoms.

7. 3-Dimethylaminopropyl triphenylphosphonium bromide hydrobromide.

8. 3-(1-Piperazinopropyl)triphenylphosphonium bromide hydrobromide.

9. A phosphorane which has the formula:

$$(R)_3P=CH—CH(R_1)CH_2A$$

wherein R is an alkyl group of 1 to 6 carbon atoms, or a phenyl, aminophenyl or benzyl group, R_1 is a hydrogen atom or an alkyl group of 1 to 6 carbon atoms and A is an amino, monoalkylamino, dialkylamino, piperidino, morpholino, piperazinyl, 4-alkylpiperazinyl, 4-hydroxyalkylpiperazinyl, 4-alkoxyalkylpiperazinyl, 4-aryloxyalkylpiperazinyl, 4-hydroxyalkyloxyalkylpiperazinyl, 4-alkylsulphonylpiperazinyl, 4-dialkylsulphamylpiperazinyl, mono-lower alkenylamino, or mono-cycloalkylamino group, said alkyl, said lower alkenyl and said cycloalkyl groups containing up to 4 carbon atoms, and said aryl groups containing 6, 7 or 8 carbon atoms.

10. A phosphorane according to claim 9, in which R is a phenyl group, R_1 is a hydrogen atom and A is an amino, monoalkylamino, dialkylamino, piperidino, morpholino, piperazinyl or 4-alkylpiperazinyl group, the said alkyl groups containing 1 to 4 carbon atoms.

11. (3-Dimethylaminopropylidene-1)triphenylphosphorane.

12. [3-(1-Piperazino)propylidene-1] triphenylphosphorane.

13. A process for the preparation of aminoalkylphosphorus compounds and their reaction products with ketones substantially as hereinbefore described with reference to the Examples.

14. Aminoalkylphosphorus compounds and their reaction products with ketones whenever prepared by a process according to any one of the preceding claims.

15. Aminoalkylphosphorus compounds according to claims 5 and 6 substantially as hereinbefore described in Examples I to VI.

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Reference has been directed in pursuance of Section 9, subsection (1) of the Patents Act, 1949, to patent Nos. 966015 and 950717.

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